

REMARKS

This is further in Response to the outstanding Final Rejection of September 22, 2004, and Applicants' Notice of Appeal of March 18, 2005. Applicants wish to supplement the record to clarify their position and to address characterizations of the cited art presented in support of the outstanding rejections.

This Request for Continued Examination includes a submission of a new claim 47, which recites objective criteria for the dissolution of a composition of the present invention. The criteria are supported by the Examples, notably Example 1, wherein it is further stated the dissolution is measured according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1N.

DeBoeck et al., USPN 5,545,628:

Applicants traverse the outstanding rejection over DeBoeck.

DeBoeck is directed to fenofibrate formulations compounded from molten fenofibrate. This necessarily excludes micronized fenofibrate as recited in claim 1. Although DeBoeck describes formulations having 5-95% fenofibrate, the reference does not teach or suggest a formulation meeting the limitations of the instant claims. DeBoeck does not teach or suggest formulations having micronized fenofibrate in an amount greater than or equal to 60% by weight and a binding cellulose derivative between 2 – 15% by weight.

In fact, DeBoeck states that an objective was the formation of a fenofibrate formulation that eliminates the need for micronization:

Accordingly, it is an object of the present invention to provide
a fenofibrate formulation not requiring use of co-micronization

which, nevertheless, exhibits a bioavailability comparable to formulations of fenofibrate which do.

It is also an object of the present invention to provide a solid, oral dosage form of a fenofibrate formulation that can be prepared by melting the excipients in which the fenofibrate is soluble and, therefore, does not require any particle size specification.

DeBoeck, column 2, lines 12-20 (emphasis added).

Further, DeBoeck states that the process is "particularly advantageous" in its simplicity; and that "[T]his renders the present manufacturing process extremely cost effective when compared to one using co-micronization of powders." DeBoeck, col. 2, lines 61-67.

DeBoeck repeatedly contrasts the disclosed formulation and method from those using micronized fenofibrate. DeBoeck repeatedly states that they deliberately sought to avoid the use of co-micronization, and that the resulting ability to compound a formulation by melting rather than co-micronization is "particularly advantageous." DeBoeck states that they were able to achieve those objectives by, among other things, resorting to the addition of specific types and quantities of, e.g., a suspension stabilizer.

The present invention is expressly limited to micronized fenofibrate. By DeBoeck's own reasoning, a formulation and method using micronization is materially distinct from that disclosed by DeBoeck. Indeed, DeBoeck teaches away from Applicants' claimed invention. It is axiomatic that a reference that teaches away from a claimed invention cannot render it obvious.

Furthermore, the outstanding rejection states that DeBoeck teaches fenofibrate formulations with high amounts of surfactants and disintegrating agents, such as polyols and poloxamers. Applicants respectfully submit that those

compounds belong to a different chemical class than the claimed hydrophilic polymers, e.g., hydroxypropylmethylcellulose (HPMC).

In DeBoeck, the polyols and poloxamers are used as a suspension stabilizer, which "avoids the formation of fenofibrate crystals during the cooling of the filled hard gelatin capsules." DeBoeck, column 2, lines 44-48. In contrast, the claimed invention uses micronized fenofibrate, for which there would be no need to avoid such crystallization, and thus there would be no motivation to add such stabilizers. Consequently, there is nothing in DeBoeck that would have motivated one of ordinary skill in the art to incorporate such stabilizers in a formulation of micronized fenofibrate.

Finally, DeBoeck discusses the use of suspension stabilizers in a molten mixture of fenofibrate-polyglycolized glycerides. The quantity of suspension stabilizer is about the same as that of the fenofibrate. In the present invention, however, the amount of surfactant is much lower than the amount of fenofibrate (e.g., about an order of magnitude). Thus, the ratios of the various components are different between DeBoeck and the present invention, and DeBoeck does not teach or suggest the claimed formulations.

Stamm et al., USPN 6,074,670:

Applicants traverse the rejection based upon Stamm.

The Stamm reference discloses an immediate release fenofibrate composition comprising:

(a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 μm , a hydrophilic polymer and a surfactant; and

(b) optionally one or several outer phase(s) or layer(s),

wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45% by weight, said hydrophilic polymer makes up from 20 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight.

The most recent Advisory Action mischaracterizes applicants' statements regarding the relevance of Stamm. Applicants did not state that the instant subject matter is not patentable absent evidence of criticality of the percentages. Quite to the contrary. Applicants quoted the MPEP stating that differences in ranges will not support patentability when subject matter is encompassed by the prior art unless the range is shown to be critical. Applicants plainly argued that such is not the case. Stamm does not encompass, nor does it abut, the claimed ranges. Thus, no showing of criticality is required.

In fact, Stamm teaches away from the claimed invention. Stamm unequivocally teaches that the hydrophilic polymer must be at least 20% by weight. (Stamm, col. 3, lines 11-23). Applicants claim that the corresponding element must be between 2 – 15% by weight. This is not only well outside the range taught by Stamm, it goes squarely against the teaching of Stamm. Thus, patentability of the claimed range does not require any showing of criticality.

The Advisory Action would ignore that teaching from Stamm. It states that Stamm teaches the same active agent and the same polymers, and then makes an

unsupported inference that Stamm encompasses the invention. But it does not. Rather, the inference and the argument ignore the plain teaching of the reference, and fail to consider the reference as a whole. The reference very plainly teaches that the immediate-release fenofibrate composition must have a hydrophilic polymer component making up at least 20% by weight. *E.g.*, col. 3, lines 12-20. There is simply nothing in the reference to the contrary that would support the rejection.

Indeed, Stamm distinguishes its formulations from those of EP 0 330 532. EP '532 describes formulations wherein fenofibrate is co-micronized with a solid surfactant, *e.g.*, sodium lauryl sulfate. According to USPN 4,895,726, which is related to EP 0 330 532, it is possible to improve bioavailability of fenofibrate to a significantly greater extent than would be achieved either by adding a surfactant, or by micronizing the fenofibrate on its own, or by intimately mixing the separately micronized fenofibrate and surfactant. USPN 4,895,726, col. 1, lines 35-43. In Stamm, co-micronization with a solid surfactant is eliminated by introducing at least 20% by weight hydrophilic polymer.

The Stamm reference does not teach or suggest formulations using less hydrophilic polymer; nor does it teach or suggest that a similar effect can be achieved by balancing less hydrophilic polymer while retaining co-micronization with some surfactant. Stamm does seem to suggest that the two phenomena can be used together, but even when combined, the reference does not suggest reducing the minimum requisite quantity of hydrophilic polymer (*i.e.*, below the stated minimum of 20 wt %). Accordingly, Stamm does not teach or suggest a micronized fenofibrate formulation comprising less than 20 wt % hydrophilic polymer, and so does not encompass (or abut) the present invention.

In view of the foregoing remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

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